REMARKS/ARGUMENTS

Applicants submit this Amendment and Reply ("Amendment") in response to the Office Action mailed on March 12, 2003. This response is being filed within two months following the three month shortened statutory period for response. A Petition for an Extension of Time of Two Months and the requisite fee accompany this Reply.

Claims 1-21 and 35-61 were pending and considered by the Examiner in his Office action. With this Amendment, claims 1, 46, and 50 have been amended and claims 6, 12, and 59 have been cancelled. Claims 62-74 have been added. Following entry of this Amendment, claims 1-5, 7-11, 13-21, 35-44, 46-58, and 60-74 are pending in the application, with claims 1, 35, 36, 39, 46, 50, 69, 70, 72 and 74 being in independent format.

Claims 1, 39, and 50 are amended for purposes of clarity and to more particularly define the subject matter of Applicants' invention by further reciting that the target tissues are selected from the group consisting of CNS tissue, heart tissue, and peripheral nervous system tissue (claims 1 and 50) and to specify a system having various components, including a controller having the capability to process acquired acoustic data and relate that data with at least one physiological tissue condition of target tissue selected from CNS, heart and peripheral nervous system tissue (claim 39). Support for these amendments to claims 1, 39, and 50 may be found throughout the specification as filed and within cancelled claims 6, 12, and 59. Claim 35 has been amended to specify monitoring at least one of a *frequency* and an amplitude of an emitted acoustic signal and relating the *frequency* of the emitted acoustic signal to a physiological tissue property. Support for this amendment may be found throughout the specification as filed, such as at page 33, lines 6-22.

Claim 45 has been cancelled without prejudice to applicants' ability to file and prosecute the same claim or similar claims in a related patent application.

Claim 46 has been amended to specify a method for localizing a physiological condition or biological response by administering ultrasound pulses to targeted tissue sites using a focused acoustic probing technique and acquiring data relating to the response induced by the focused acoustic probing. This technique may be used, for example, to identify and localize sites of

generalized, undifferentiated pain within enlarged or abnormal tissue sites. This aspect of applicants' claimed invention is described throughout the specification, as filed, such as at page 18, line 20 - page 19, line 25. Claims 51, 52, 54, 55, 58 and 61 have been amended to recite multiple dependencies.

Claims 62-74 have been added. Claim 62 is dependent from claim 35 and specifies that the target tissue is CNS and the physiological parameter is ICP. Claims 63 and 64 specify two methods for oscillating target tissue by applying a known acoustic radiation force using at least two acoustic sources having specified output characteristics. These aspects of applicants' claimed invention are described in the specification, for example, at page 53, lines 28-31. Claim 65 is dependent from claim 50 and recites that the target tissue is CNS and the tissue property determined is ICP.

Claims 66 and 67 depend from claim 39 and specify that the controller is capable of processing acoustic data acquired from CNS target tissue and relating it to at least one of ICP, ABP and CPP (claim 66) or ICP (claim 67). This aspect of applicants' claimed invention is described in the specification, for example, at the paragraph spanning pages 19 and 20. Claim 68 depends from claim 67 and specifies that the controller is capable of processing acoustic data acquired from CNS target tissue and ABP data and relating those data to ICP. This aspect of applicants' claimed invention is described in the specification, for example, at page 23, lines 9-12.

Newly added claim 69 recites a method for assessing a physiological property of a CNS, heart or peripheral nervous system target tissue involving acquiring acoustic data relating to a biological response of an intrinsic or induced tissue displacement using an ultrasound transducer and relating the acoustic data with a physiological property of the target tissue. This aspect of applicants' claimed invention is described in the specification, for example, at page 20, lines 11-22. Claim 70, which is dependent from claim 69, specifies acquiring acoustic data relating to at least one of changes in local perfusion rate, flood flow velocity, and electrophysiological activity. This aspect of applicants' claimed invention is described in the specification, for example, at page 21, lines 24-27.

Newly added claim 71 specifies a method for assessing ICP comprising collecting acoustic data relating to intrinsic tissue displacements at one or more CNS sites at multiple time points

over the course of at least one cardiac cycle using an ultrasound transducer and relating the acoustic data with ICP. Claim 72 specifies a method for assessing ICP comprising collecting acoustic data relating to a biological response of an intrinsic or induced CNS tissue displacement using an ultrasound transducer and relating to the acoustic data with ICP. Claim 73 depends from claim 72 and recites collecting acoustic data relating to blood flow velocity from a CNS site and relating the acoustic data with ICP. These aspects of applicants' claimed invention are disclosed throughout the application as filed.

Claim 74 recites a method for assessing a physiological parameter of a target tissue that includes characterizing the acoustic propagation environment by conducting an initial environmental assessment to determine the location and properties of tissue between an acoustic source and the garget tissue. This aspect of applicants' invention is described in the specification, for example, at page 53, lines 20-28.

It is urged that no new matter has been introduced to the application.

Patentability under 35 U.S.C. § 102.

Claims 1-5, 14-15, 20-21, 35, 39-42, 45-46, and 50-57 were rejected under 35 U.S.C. § 102 as allegedly anticipated by Walker et al., U.S. Patent No. 6,039,691 ("Walker"). The Examiner alleges that Walker teaches, by reference to Figure 1, a system for assessing a physiological parameter of a target tissue comprising an acoustic source and detector operably connected to a power source, the power source being operably connected to a function generator, and the function generator being operably connected to a controller inherently comprising structures for data acquisition, storage and analysis, processing acquired data and relating the acquired acoustic data with at least one physiological tissue condition, wherein the controller is operably connected to a display device for displaying information relating to at least one physiological tissue condition. The Examiner further alleges that Walker teaches that the acoustic source is an ultrasound transducer and that the transducer is operative in a Doppler mode. Because Walker is said to meet all these claimed structures, the Examiner alleges that "the method concerning the steps of inducing a tissue displacement by applying an ultrasound energy, noninvasively acquiring data, applying plurality of different pulses, inducing oscillation of the target tissue, etc. are inherently met by the disclosure."

Applicants respectfully traverse the stated grounds of rejection and submit that Walker does not anticipate nor render obvious any of the claims, as presently amended, because Walker does not teach each element of any of the pending claims, nor does Walker suggest the applicants' claimed invention as set for in the pending claims.

Walker et al. is directed to an ultrasonic transducer system for generating a series of ultrasound pulses, at least one of which is of sufficiently high intensity to induce physical displacement of a soft tissue. The apparatus and methods described by Walker et al. are said to be employable in examining the properties of a subject's vitreous body and, thus, may be useful in the evaluation and/or diagnosis of ocular disorders, such as vitreous traction. (*See*, Abstract). As defined in the specification, "soft tissue" is meant to encompass tissue, such as the vitreous body, "having a modulus of elasticity of less than 5.0 N/m^2, and typically between about 0.1 N/m^2 to about 3.5 N/m^2." (*See*, Column 3, lines 16-21 and Column 6, lines 36-40). Cervical mucus is exemplary of other types of soft tissue that may be examined using the methods of Walker et al.

Independent claim 1, as amended, and claims 2-5, 14-15, and 20-21, which depend therefrom, are directed, *inter alia*, to a method for detecting a physiological property of a target tissue, wherein the target tissue is selected from the group consisting of CNS tissue, heart tissue, and peripheral nervous system tissue. CNS tissue, heart tissue and peripheral nervous tissue all have a modulus of elasticity well outside the range assigned by Walker et al. to "soft tissue" of the type his methods and systems are suitable for use with. Francis Duck, *Physical Properties of Tissue: a Comprehensive Reference Book*, Academic Press, London (1990), indicates that the "Young's Modulus," or modulus of elasticity for tissue is generally in the range of $10^3 - 10^6$ N/m^2. This reference also indicates that an exemplary "Young's Modulus," or modulus of elasticity for an artery wall is 1×10^6 N/m^2. A copy of relevant portions of this reference will be provided to the Examiner shortly for his review.

The use of acoustic examination techniques for tissues having a modulus of elasticity several orders of magnitude different from that of the vitreous body and cervical mucus tissue disclosed by Walker et al. certainly were not disclosed and, it is urged, were not contemplated by Walker et al. There could be no reasonable expectation that the apparatus and method disclosed by Walker et al. would have any application whatsoever to CNS, heart and peripheral nervous

tissue having a modulus of elasticity several orders of magnitude different from that of the biological tissue disclosed by Walker et al.

Independent claim 35 is directed to methods for assessing a physiological parameter of a target tissue comprising, *inter alia*, inducing oscillation. Claim 35 has been amended to specify that the frequency of the induced oscillation is measured and related to a physiological tissue property. In contrast, and as noted above, Walker et al. teaches the use of ultrasound to induce physical displacement of a soft tissue and then images the displacement. Oscillation may be broadly viewed as a series of physical displacements that occur with a specified periodicity. Note, however, that claim 35 specifies measurement of the *frequency of induced oscillation*. Walker et al. is clearly inducing and measuring *tissue displacement* rather than the *frequency of induced oscillation*. Walker et al. does not teach or suggest the use of ultrasound to induce oscillation of any tissue, nor does Walker et al. teach or suggest the determination of the frequency of induced oscillation. It is urged that this claim rejection must be withdrawn.

Independent claim 39, and claims 40-42 which depend therefrom, are directed to a system having a controller capable of processing acoustic data and relating it with at least one physiological tissue condition of target tissue selected from the group consisting of CNS tissue, heart tissue and peripheral nervous system tissue. Walker et al. does not teach or suggest a system having this capability. As described above, the Walker et al. methods and system are described only with reference to the examination of "relatively soft biological tissue," which is defined as having a specified modulus of elasticity which is orders of magnitude different from the modulus of elasticity of the tissues to which applicants' claims pertain. It is urged, therefore, that claims 39-42 are not anticipated by Walker et al.

Independent claim 46, as presently amended, is directed, *inter alia*, to a method for localizing a physiological condition or biological response comprising administering ultrasound pulses to a plurality of targeted tissue sites using a focused acoustic probing technique, and acquiring data relating to the physiological condition or biological response induced by the ultrasound pulse(s) at each of the targeted tissue sites. Walker et al. do not disclose or suggest methodologies for localizing a physiological condition or biological response by administering ultrasound pulses to a plurality of targeted tissue sites using a focused acoustic probing technique. Applicants' methodology and focused acoustic probing technique is used, for

example, to localize the source of a biological response, such as pain, within a generalized site of undifferentiated pain. This aspect of applicants' invention is described in the specification, for example, at pages 18, line 9 – page 10, line 25. Applicants do not perceive that Walker et al. discloses or suggests any such methodology.

Independent claim 50, as presently amended, and claims 51-57, which depend therefrom, is directed, *inter alia*, to a method for assessing a physiological property of a target tissue wherein said target tissue is selected from the group consisting of CNS tissue, heart tissue, and peripheral nervous system tissue. Because Walker does not teach detecting a physiological property of any of these tissues, Walker does not disclose each element of any of these claims; therefore, Walker does not anticipate any of claims 50-57.

Because Walker, et al. do not anticipate any of Applicants' pending claims, Applicants respectfully request reconsideration and withdrawal of the Examiner's outstanding rejection.

Patentability under 35 U.S.C. § 103.

Claims 6-13, 16-19, 36-38, 43-44, 47-49, and 58-61 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Walker et al. in view of Madsen et al., U.S. Patent No. 6,086,533 ("Madsen") or Mick, U.S. Patent No. 5,074,310 ("Mick"). The Examiner alleges that Walker et al. teaches each limitation of the cited claims with the exception that it fails to disclose that the ultrasound transducer is used for measuring intracranial pressure. Madsen and Mick are cited in the alternative for allegedly remedying this deficiency in the Walker et al. reference. More specifically, the Examiner cites Madsen for allegedly teaching a pressure transducer to noninvasively measuring intracranial pressure of a patient and cites Mick for allegedly teaching a transcranial Doppler transducer for noninvasively measuring the intracranial pressure of a patient. The Examiner alleges that Madsen or Mick evidence that one of ordinary skill in the art would recognize the benefit of using a transcranial Doppler transducer. Thus, the Examiner alleges that it would have been obvious to modify the ultrasound system of Walker to include a trancranial Doppler transducer for the non-invasive measurement of intracranial pressure of a patient.

Applicants note that, with the present Amendment, claims 6, 12, and 59 are now cancelled from the application thereby obviating the present bases for rejection as to these

claims. Applicants respectfully traverse the stated grounds of rejection as they apply to the pending claims and submit that the presently claimed invention is non-obvious over Walker et al. in view of Madsen and/or Mick because these references, viewed as a whole, neither teach nor suggest the subject matter set forth in any of Applicants' claims 7-11, 13, 16-19, 36-38, 43-44, 47-49, 58, and 60-61.

As discussed above, Walker et al. teach an ultrasonic transducer system for generating a series of ultrasound pulses, at least one of which is of sufficiently high intensity to induce physical displacement of a soft tissue. More specifically, the apparatus and methods of Walker are said to be employable in examining the properties of a subject's vitreous body and, thus, may be useful in the evaluation and/or diagnosis of ocular disorders, such as vitreous traction. Walker contrasts "soft tissue" such as vitreous body, with "other body tissues" (Column 3, line 18) and explicitly defines "soft tissue" as a tissue "having a modulus of elasticity of less than 5.0 N/m^2, and typically between about 0.1 N/m^2 to about 3.5 N/m^2." As discussed above, the methods and systems of the present invention are intended, and claimed, for use in connection with tissues having a modulus of elasticity several orders of magnitude different from the modulus of elasticity for soft tissue defined by Walker et al.

Walker et al. neither teach nor suggest using an ultrasonic transducer system to induce physical displacement of a tissue selected from the group consisting of CNS tissue, heart tissue, and peripheral nervous system tissue or tissue sites selected from the group consisting of CNS tissue sites, heart tissue sites, and peripheral nervous system tissue sites. Nor does Walker et al. teach or suggest using an ultrasonic transducer system to acquire acoustic data relating to intrinsic tissue displacements in target tissue sites including CNS, heart and peripheral nervous system tissue. There is no motivation that suggests using the method and system disclosed by Walker et al. for tissues having different properties than the "soft tissue" specifically defined in Walker et al., nor would there be any expectation of success based on the teachings of Walker et al., or elsewhere to applicants' knowledge, for using the methods and systems of applicants' claimed invention.

Neither Madsen et al. nor Mick remedy the deficiencies in the Walker reference with respect to applicants' claimed invention. Madsen et al. discloses the non-invasive measurement of blood velocity and correlation of such measurements with externally applied pressure to detect

and/or assess diseases or physiological abnormalities, such as hydrocephalus, retinopathy, papilledema, and the like. Madsen et al. indicate that for some applications, measurements of the ophthalmic region may be used to detect intracranial abnormalities, particularly in adults whose fontanelle regions have fused. These are in vivo pressure measurements that involve measurement of an externally applied pressure – a pressure applied by a pressure applicator at a target region. Applicants do not perceive how the combination of Madsen et al. with Walker et al. would result in a modification of Walker et al. for measurement of ICP noninvasively.

Mick discloses a method for non-invasively measuring changes in ICP, permitting diagnoses of ICP trends over time. A vibration is applied to a skull in one location, and an output vibration (spectral response data) is detected from another location on the skull. This methodology is based on the principal that the dynamic vibration characteristics and behavior, natural frequency, mechanical impedance, coherence characteristics, and frequency response spectrum of a material (bone in this case) changes in relation to the stress applied to the elastic material. See Col 4, lines 29-35. Mick is measuring the characteristics of mechanical vibration of the skull, such as the frequency response to the applied vibration, and correlating them with changes in ICP over time.

Applicants do **not** encompass the bony portion of the skull within their use of the term "CNS tissue." The term "central nervous system" (CNS) is generally used to refer to the brain and spinal cord, as well as the cranial nerves. The specification, at page 21, lines 11-13, states that brain tissue, and other CNS tissue, including, e.g., CSF, tissue adjacent to CSF (cerebrospinal fluid) or brain parenchyma, cranial nerves such as the optic nerve, and the like, are suitable target tissue sites for assessment of ICP. At page 24, lines 13-21, the specification states that non-ventricular CNS target sites are preferred for many applications, while ventricular sites, such as CNS sites in proximity to a fluid storage site, the choroids plexus, the spinal column, and the like are suitable CNS target sites in other circumstances.

It is thus clear, even with respect to CNS target tissues, CNS target tissue sites, and assessment of ICP, that Mick does not overcome the deficiencies of Walker et al., nor of any combination of Walker et al. with Madsen et al. Applicants do not perceive that there is any combination of these references that would suggest, or provide the motivation for, or lead to a reasonable expectation of success, of applicants' claimed invention.

Applicants' claims 47-49 relate to a method for localizing a physiological condition or biological response by administering ultrasound pulses to a plurality of targeted tissue sites using a focused acoustic probing technique and, for example, observing the subjective sensation of pain induced. This methodology may be used, for example, to pinpoint specific origins of pain. Applicants do not perceive that the use of a focused acoustic probing technique to localize such a physiological condition, or related biological response, is suggested by any combination of any of the references relied upon for rejection.

It is urged that applicants' pending claims are in condition for allowance. Early reconsideration and allowance of the pending claims is respectfully requested. Should the Examiner continue to have any concerns about the pending claims, he is invited to telephone the applicants' representative at the number listed below.

Respectfully submitted,

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